Activation of the alternative NF-κB pathway improves disease symptoms in a model of Sjogren's syndrome.

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Abstract:

The purpose of our study was to understand if Toll-like receptor 9 (TLR9) activation could contribute to the control of inflammation in Sjogren's syndrome. To this end, we manipulated TLR9 signaling in non-obese diabetic (NOD) and TLR9(-/-) mice using agonistic CpG oligonucleotide aptamers, TLR9 inhibitors, and the in-house oligonucleotide BL-7040. We then measured salivation, inflammatory response markers, and expression of proteins downstream to NF-κB activation pathways. Finally, we labeled proteins of interest in salivary gland biopsies from Sjogren's syndrome patients, compared to Sicca syndrome controls. We show that in NOD mice BL-7040 activates TLR9 to induce an alternative NF-κB activation mode resulting in increased salivation, elevated anti-inflammatory response in salivary glands, and reduced peripheral AChE activity. These effects were more prominent and also suppressible by TLR9 inhibitors in NOD mice, but TLR9(-/-) mice were resistant to the salivation-promoting effects of CpG oligonucleotides and BL-7040. Last, salivary glands from Sjogren's disease patients showed increased inflammatory and decreased anti-inflammatory biomarkers, in addition to decreased levels of alternative NF-κB pathway proteins. In summary, we have demonstrated that activation of TLR9 by BL-7040 leads to non-canonical activation of NF-κB, promoting salivary functioning and down-regulating inflammation. We propose that BL-7040 could be beneficial in treating Sjogren's syndrome and may be applicable to additional autoimmune syndromes.

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